

## The BATTLE to Personalize Lung Cancer Prevention through Reverse Migration

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### Abstract

Agents can enter clinical development for cancer prevention either initially or after previous development for a different indication, such as arthritis, with both approaches consuming many years of development before an agent is fully evaluated for cancer prevention. We propose the following, third approach: reverse migration, that is, importing agents, targets, and study designs to personalize interventions and concepts developed in advanced cancer to the setting of cancer prevention. Importing these "ready-made" features from therapy will allow reverse migration to streamline preventive agent development. We recently reported the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial of personalized lung cancer therapy and now propose the reverse migration development of personalized lung cancer prevention based on the BATTLE model. *Cancer Prev Res*; 4(7); 962–72. ©2011 AACR.

### Introduction

Chemoprevention has produced notable successes in delaying or preventing cancer and/or carcinogenesis (1–16), but progress has been slow. The suitability and selection of potential chemopreventive agents for clinical development are determined by epidemiologic and pre-clinical studies (17–20). Agents can enter clinical development for cancer prevention either initially or after previous development for a different indication. The former approach historically has involved mostly natural agents, although a recent such study in early phases is simultaneously developing targeted agents for prevention and therapy (21). Examples of the latter approach include celecoxib, which was developed initially for arthritis and subsequently for cancer prevention in the colon, lung, bladder, and other sites; metformin, developed for diabetes and currently being studied in preclinical models of carcinogenesis (e.g., colon, breast, and lung) and in clinical cancer prevention trials in the breast, uterus, colon, and prostate; and finasteride and dutasteride, developed for

benign prostatic hypertrophy and subsequently for prostate cancer prevention (22–25). Both of these clinical approaches consume many years of development before an agent is fully evaluated for cancer prevention. We propose the following third approach, which has the potential to streamline the development process: reverse migration, that is, importing agents, targets, study designs, and concepts developed in advanced cancer to the setting of cancer prevention. The most striking example of an *ad hoc* reverse migration is in breast cancer, where the same agent, tamoxifen, was initially used as therapy for metastatic disease, then as adjuvant therapy, and then as prevention (Table 1). We now propose reverse migration as a prespecified approach for cancer prevention drug development, with the capacity to streamline this development via the advantages of identifying candidate agents and molecular targets and other lessons learned in cancer therapy.

Prevention can target different groups of patients. According to one set of definitions, primary chemoprevention focuses on noncancer individuals at a high risk of cancer, for example, current or former smokers; secondary chemoprevention focuses on patients with precancerous lesions, and tertiary chemoprevention focuses on patients with a cancer history and at risk of recurrent or second primary tumors (SPT).

At the heart of cancer prevention are the principles of field cancerization and multistep carcinogenesis. Field cancerization is the idea that injury from a carcinogen occurs throughout a field such as the aerodigestive tract, and carcinogenesis can occur at multiple sites within this exposed field (26). This phenomenon was first described in the oral cavity, based on light microscopy observations of histopathology, but we now know that molecular changes occur in normal appearing epithelium adjacent to tumors (27–29). Multistep carcinogenesis was first described by

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**Table 1.** The reverse migration of tamoxifen

	Treatment setting	Results
Tamoxifen vs. DES, 1981 (114)	Metastatic disease <sup>a</sup>	Response rate 33% on tamoxifen monotherapy
EBCTCG meta-analysis, 1998 (115)	Adjuvant treatment	47% decrease in recurrence with 5 y of tamoxifen vs. placebo
B-24, 1999 (116)	DCIS	43% decrease in IBC, 32% decrease in NIBC with tamoxifen vs. placebo
BCPT, 1998 (5)	Healthy, moderate-risk women	49% decrease in IBC, 40% decrease in NIBC with tamoxifen vs. placebo

Abbreviations: BCPT, Breast Cancer Prevention Trial; DES, diethylstilbestrol; DCIS, ductal carcinoma *in situ*; EBCTCG, Early Breast Cancer Trialists' Collaborative Group; IBC, invasive breast cancer; NIBC, noninvasive breast cancer.

<sup>a</sup>Hormone receptor status was not measured prior to enrollment on trial.

Auerbach and colleagues, who reported serial changes in the lungs of smokers, with a progression from hyperplasia to metaplasia to dysplasia to carcinoma *in situ* to cancer (Fig. 1; refs. 30, 31). Early events in carcinogenesis also occur at the molecular level—accumulating genetic and epigenetic events are necessary to induce phenotypical changes.

To date, large-scale lung cancer chemoprevention trials have shown negative results: neutral or even harmful (18, 32–34). Lacks of predictive and risk biomarkers and of a high-risk cohort certainly contributed to the negative results of these trials. Furthermore, these trials did not recognize the differences between tumors in current smokers versus former smokers versus never smokers. Current smokers seemed to be harmed by some interventions, including 13-*cis*-retinoic acid,  $\beta$ -carotene, and possibly vitamin A, whereas they were associated with a trend toward benefit in former and never smokers (32, 34). These contrasting results hinted at the biological differences now known to exist in tumors in these different patient populations (35, 36).

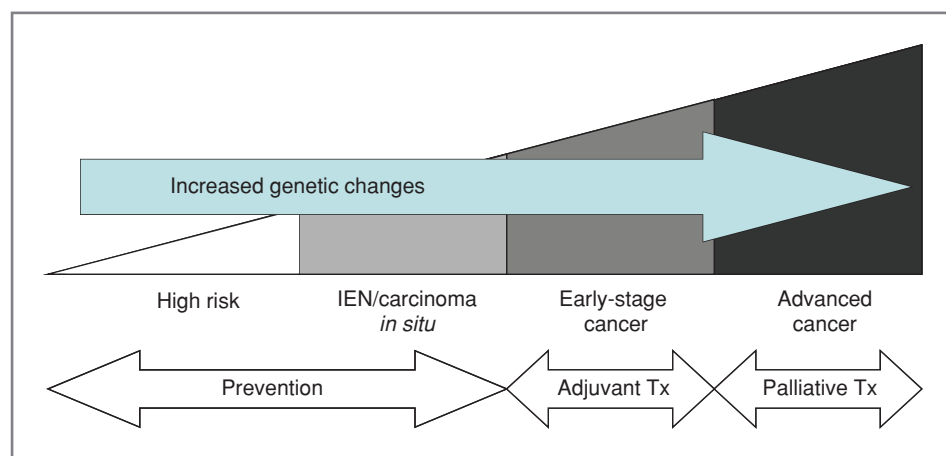
Positive chemoprevention trials differ from negative ones in important ways besides outcome. Positive trials usually involve targets, such as hormone receptors in breast

and prostate cancer and inflammation in colon cancer, that can be inhibited effectively by drugs, or they target infections, such as viruses leading to hepatocellular or cervical cancer, that can be controlled by interventions such as vaccines. Many negative trials have used natural agents identified in epidemiologic studies, such as  $\beta$ -carotene (18) and vitamin E (17), without a clear target. Recent data suggest the potential to improve on this track record by personalizing diet-related interventions (37, 38).

#### Barriers to lung cancer chemoprevention

To date, there are no known effective chemoprevention agents for lung cancer. Previous trials in lung cancer chemoprevention have been negative for several reasons. Lung cancer is complex, beginning with its different histologic subtypes of non-small-cell carcinoma, such as adenocarcinoma and squamous cell carcinoma, and small-cell carcinoma. Furthermore, neoplastic areas in a patient's lungs are not homogeneous and have regional variation (39). We have a very limited understanding of the presumably multiple, complex, histologic and molecular pathways leading to each subtype of lung cancer, and histologic precursors of squamous cell carcinoma (generally occurring in the central/proximal lung) are the best understood (40–42).

**Figure 1.** Schema showing progression from high-risk states to advanced lung cancer, correlating with increased genetic changes, and the treatment (Tx) options at each stage. Intraepithelial neoplasia (IEN) includes hyperplasia, metaplasia, and dysplasia.



Tumors of other organ sites are molecularly heterogeneous as well, but we have a better understanding of the molecular drivers of at least a subset of some of these tumors, for example, hormone receptor-positive breast cancer. Mouse models for lung premalignancy are in active development, with most such work focused on genetically engineered models of lung adenocarcinoma (e.g., building on the *KRAS* transgenic model; ref. 20). Because of our limited (but increasing) understanding of the biology of lung tumors, targeted agents have been only moderately effective in the treatment of this disease and do not yet have a role in its prevention. Epidemiology attempts to identify agents that ultimately proved to be clinically effective have been unsuccessful thus far. The optimal endpoints for lung cancer prevention trials have yet to be determined; the traditional endpoints in cancer incidence and survival require long, expensive follow-up.

Several recent studies with targeted agents, smaller patient cohorts, and biomarker-related endpoints are steps toward bridging the gap between traditional chemoprevention trials with epidemiologically identified agents administered to large, unselected cohorts and personalized prevention. Some recent randomized trials have focused their efforts on former smokers, as several large studies, described in Table 2, have suggested that chemoprevention may cause differential effects between current and former smokers. Kurie and colleagues were the first to target former smokers alone and found promising results in the modulation of retinoic acid receptor- $\beta$  (43). These findings were followed by a study led by Kim and colleagues showing that cyclooxygenase-2 (COX-2) inhibition with high-dose celecoxib (400 mg twice daily) decreased Ki-67 labeling

(compared with placebo) in the bronchial epithelium of current and former smokers, with a greater magnitude in former smokers (44); results were confirmed and extended in a large, randomized study in former smokers by Mao and colleagues (45). Mao et al. also identified a high ratio of COX-2 to 15-hydroxyprostaglandin dehydrogenase (15-PGDH) mRNA in bronchoalveolar lavage cells as a predictive marker of the efficacy of celecoxib (45). High Ki-67 at baseline also predicted response. Celecoxib also reduced levels of IL-6 (45), which is a key inflammatory mediator of lung carcinogenesis (46). Most recently, Keith and colleagues completed a randomized controlled trial of oral iloprost that found improved histopathology in serial bronchoscopies in former smokers (47). Further evidence of the efficacy of COX inhibition in chemoprevention came from a recent meta-analysis of randomized trials for vascular disease prevention showing that daily aspirin treatment is associated with a decrease in mortality from lung adenocarcinoma and a number of other cancers (48).

A trial of inhaled budesonide did not achieve an improvement in its primary endpoint of radiographic abnormalities but still can serve as a model for future prevention studies in adenocarcinoma (which generally occurs in the peripheral lung fields) incorporating radiographic endpoints (49). This trial's design may become very useful for prevention trials in this patient population because its screening approach [spiral computed tomography (CT)] will become very widespread clinical practice after the positive results of the National Lung Screening Trial (NLST) showing that spiral CT screening resulted in 20.3% reduction in lung cancer mortality (vs. standard

**Table 2.** Relevant randomized controlled trials in lung cancer chemoprevention highlighting differences between current and former smokers

Trial	Population	Intervention	Endpoint	Outcome—current smokers	Outcome—former smokers
ATBC, 1994 (18)	Male current smokers	$\alpha$ -Tocopherol, $\beta$ -carotene	Lung cancer	Increase in lung cancer	N/A
CARET, Omenn et al., 1996 (32)	Smokers (current or former)	$\beta$ -Carotene, retinol palmitate	Lung cancer	Increase in lung cancer	Trend toward decrease in lung cancer
Lippman et al., 2001 (34)	Following resection of stage I NSCLC	13- <i>cis</i> -RA	Survival	Decreased survival	Trend toward increased survival <sup>a</sup>
Kurie et al., 2003 (43), Hittelman et al., 2007 (117)	Former smokers	9- <i>cis</i> -RA or 13- <i>cis</i> -RA plus $\alpha$ -tocopherol	RAR- $\beta$ , Ki-67, and metaplasia	N/A	Increase in RAR- $\beta$ and decrease in Ki-67
Mao et al., 2011 (45)	Former smokers	Celecoxib	Ki-67 labeling index	N/A	Decrease in Ki-67
Keith et al., 2011 (47)	Smokers (current or former)	Oral iloprost	Endobronchial dysplasia	No histologic improvement	Improvement in histology

Abbreviations: 9-*cis*-RA, 9-*cis*-retinoic acid; 13-*cis*-RA ATBC, 13-*cis*-retinoic acid; Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CARET, Carotene and Retinol Efficacy Trial; RAR- $\beta$ , retinoic acid receptor- $\beta$ .

<sup>a</sup>Nonsmokers enrolled on this trial had a trend toward lower death rate with 13-*cis*-RA vs. placebo: 2% vs. 5.2%,  $P = 0.14$ .

X-ray), thus identifying many patients with nodules who could be candidates for prevention.

### Moving from personalized therapy to personalized prevention: reverse migration

The backbone of treatment of advanced lung cancer is cytotoxic therapy with platinum-based doublets (50–52), although response and survival rates are low. Our understanding of the molecular biology of lung cancer is improving, and this improvement is facilitating the increasing clinical use of targeted therapies for this disease. Building on the increased use of targeted therapies, recent studies are attempting to personalize cancer treatment.

One important such personalizing study is our recently reported Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial (53). Patients with advanced lung cancer underwent a core needle biopsy. This biopsy was analyzed for biomarkers that were used in constructing a biomarker profile. This profile determined which of various treatment groups the patient was placed into. The BATTLE hypothesis was that individual lung tumors are driven by a predominant

signaling pathway from among the multiple altered signaling pathways in lung cancer overall and that this pathway could be targeted. We employed a novel Bayesian adaptive randomization design in testing multiple agents, identifying predictive markers, and increasing the number of patients receiving effective treatment. BATTLE showed the feasibility of a biopsy-mandated approach and has provided a wealth of hypothesis-generating data, such as the intriguing finding of a relatively high disease control rate with sorafenib in patients with *KRAS* mutations, for further study.

As in treating advanced lung cancer, it is unlikely that any single agent will be universally effective in preventing lung cancer. To make an impact, we must personalize lung cancer therapy and prevention.

### Molecular abnormalities and targeted therapy in lung cancer

We know several of the molecular abnormalities that lead to and drive lung cancer (Fig. 2). Molecular abnormalities are different in smokers versus nonsmokers and in adenocarcinomas versus squamous cell carcinomas.

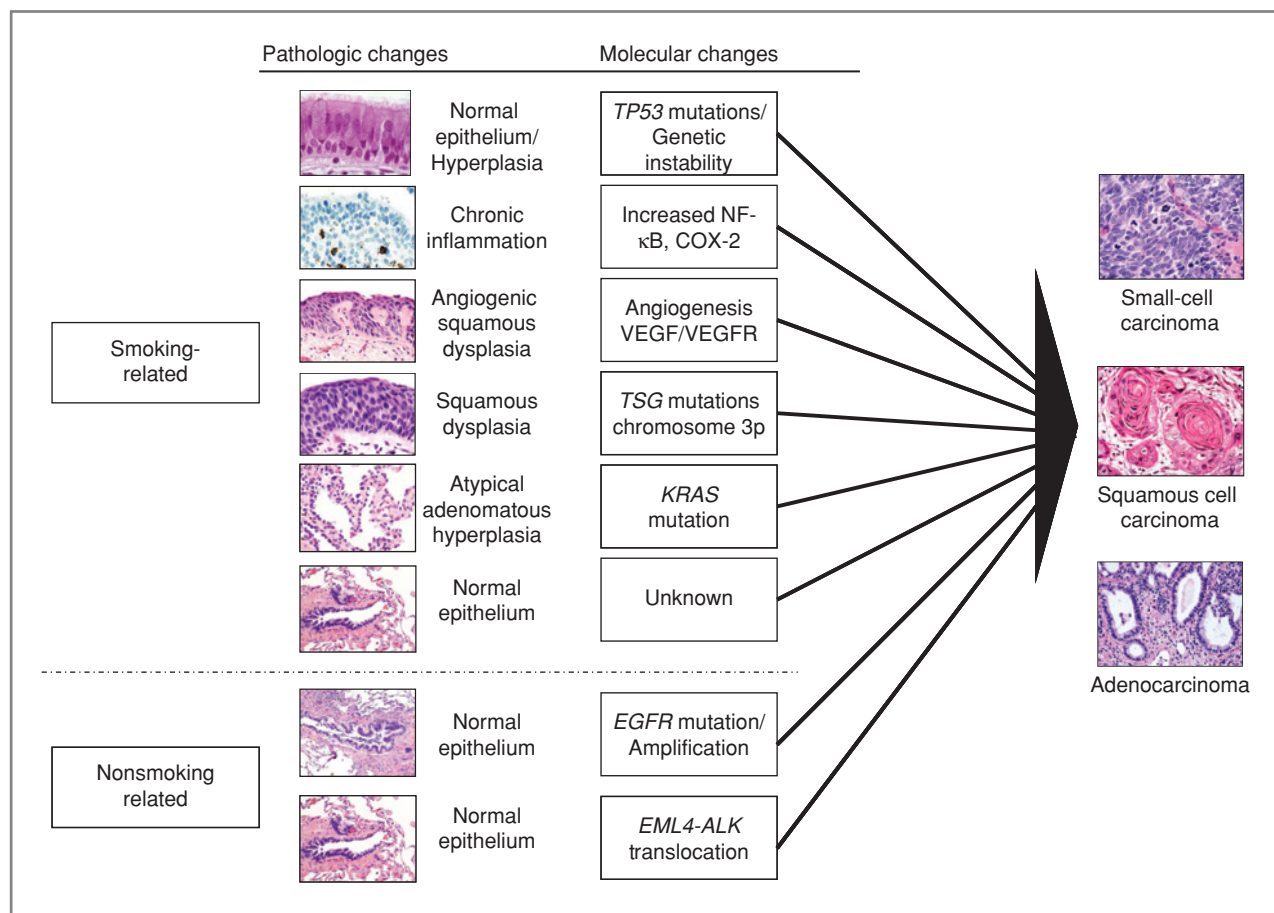


Figure 2. Schema showing some of the different histopathologic and molecular pathways involved in lung carcinogenesis. NF- $\kappa$ B, nuclear factor kappa B; TSG, tumor suppressor gene.

Mutations in tumor suppressor genes such as *TP53* are early events of lung squamous cell carcinoma (41, 54). Inflammatory markers are frequently seen in precursors to squamous cell carcinoma, and upregulation of COX-2 predicted for benefit from celecoxib combined with chemotherapy in one study, suggesting that at least a group of tumors are "addicted" to this pathway (55, 56). *KRAS* mutations are often seen in atypical adenomatous hyperplasia, which is a probable precursor to a small subset of adenocarcinoma (41, 54). These mutations occur in up to 30% of adenocarcinomas, most often in current or former smokers (54, 57, 58), and are associated with resistance to epidermal growth factor receptor (EGFR) inhibition (59). *EGFR* mutations occur in approximately 10% of adenocarcinomas in Western countries and in a higher percentage in Asia; these mutations seem to be early events in carcinogenesis, found in histologically normal epithelium (preceding *EGFR* amplification) adjacent to lesions (39, 60–62). Patient tumors with *EGFR* mutations often respond well to EGFR inhibition (60). Mutations in *LKB1* are common in adenocarcinoma and may predict for resistance to mTOR inhibitors (40, 63, 64). Echinoderm microtubule-associated protein-like 4 (*EML4*)-anaplastic lymphoma kinase (*ALK*) translocations have been described in 5% to 7% of Asian lung cancer patients and in 13% of a clinically selected group of U.S. lung cancer patients (65–67). In early-phase trials, these patients seem to be highly sensitive to an oral *ALK* inhibitor (68). Activations in the phosphoinositide 3-kinase (PI3K) pathway are seen in early carcinogenesis (69) and *PI3K* mutations are important to lung tumor biology (70). Mutations in *BRAF* are found in lung cancer, and trials with *BRAF* inhibitors are ongoing (71). The first potential driver mutations (in the *DDR2* kinase gene) in lung squamous cell carcinoma were identified recently (72). Further study will be needed to evaluate these markers in premalignancy.

#### Personalized prevention: the BATTLE is on

We propose the reverse migration of findings on biomarkers, pharmacogenomics, and targeted therapies from the metastatic setting to the chemoprevention setting. By incorporating risk assessment using both molecular and clinical characteristics, biomarker analyses, targeted agents, predictive markers, measurement of the target inhibition, and surrogate endpoints, future chemoprevention trials will be able to personalize their interventions.

Prognostic or risk markers are critical for the design of future chemoprevention studies because identifying high-risk populations facilitates every aspect of a trial, from the logistics of its size, duration, and cost to monitoring intervention activity to producing a result that can be translated into standard clinical care. These markers are less critical for therapy trials in advanced disease because the poor prognosis of their trial populations is generally known; BATTLE, for example, enrolled chemorefractory metastatic lung cancer patients, who have a universally grim prognosis. There are 3 lung cancer risk models based on clinical/demographic factors (the Spitz, Bach, and Liver-

pool models) and which have limited effectiveness in identifying populations at high risk; attempts to enhance the models by integrating various single nucleotide polymorphisms [(SNP); e.g., involving the nicotine receptor and human telomerase reverse transcriptase (hTERT)] have had limited success in improving the models (73). New risk models should incorporate molecular somatic/tissue markers to identify patients at the highest cancer risk for chemoprevention efforts (74–77). For example, LOH profiles are markers of a high cancer risk in oral premalignancy (78) and are being used in the ongoing Erlotinib Prevention of Oral Cancer (EPOC) trial. Recent data suggest the potential to use C-reactive protein to identify individuals who may develop celecoxib-associated cardiovascular toxicity (79). Finding markers such as this, which predict an increased likelihood for adverse events rather than a decreased efficacy, is an important, underappreciated issue for personalized medicine.

Molecular epidemiology is also beginning to identify germ line markers that predict benefit from specific therapies. SNPs have been identified (notably involving *PI3K* pathway genes) that predict risk (untreated) and benefit from retinoids in head and neck cancer (80) and from bacillus Calmette–Guérin in early-stage bladder cancer (81). SNPs within the 3-hydroxy-3-methyl-glutaryl-Co-A (*HMG Co-A*) reductase gene are associated with a reduction in colon cancer risk in people using statins (82), and polymorphisms in cytochrome P450 2C9 (*CYP2C9*) predict for both benefit and harm (adverse cardiovascular effects) from high-dose celecoxib (83). A recent pharmacokinetics study identified a SNP region containing the *ATM* tumor suppressor gene that influenced the response to metformin, suggesting the potential to personalize metformin prevention (84).

Valid targets and effective targeted therapies in advanced cancer should be studied in chemoprevention trials that include biomarker profiling and endpoints. Although targeted therapies in lung cancer have been shown thus far only to be effective in advanced disease (85–87), they can improve outcome in the adjuvant setting (as well as advanced disease) in other tumor types (88). mTOR inhibition with the rapamycin analogues (rapalogues) temsirolimus and everolimus is effective in treating renal cell carcinoma (89, 90); in preclinical models, rapalogues are active against lung premalignancy (91). Unfortunately, drugs in this class can cause the paradoxical activation of survival pathways by release of feedback inhibition (92), and many of these drugs are not well tolerated in long-term treatment. The mTOR inhibitor metformin is a well-tolerated potential chemopreventive agent that does not cause activation of survival pathways, in contrast to the rapalogues, and has preventive activity in preclinical models of lung carcinogenesis (23, 24).

An important element for future prevention trials is to determine that the intervention is modulating its target during the trial. For example, monitoring prostaglandin metabolites in urine can determine whether COX-2 inhibitors are indeed modulating COX-2 in specific

individuals and thus possibly identifying which individuals will derive benefit from these agents (93). *myo*-Inositol suppressed dysplastic lesions in patients with activation of the PI3K/phosphorylated Akt (pAkt) pathway in association with suppression of pAkt (94) and a PI3K pathway activation signature (69). Monitoring circulating levels of cytokines and angiogenic factors may help identify which individuals will derive benefit from VEGF inhibitors (95–97). Potential surrogate endpoints for trials involving erlotinib or bexarotene could be rash or hypertriglyceridemia, respectively (98, 99). Perhaps, future lung cancer prevention trials could monitor telomere length, as telomere shortness is associated with smoking and cancer risk (100, 101). Predictive markers for chemoprevention are limited. Data from trials with celecoxib and iloprost clearly identify former smokers as a target population for agents targeting arachadonic acid metabolism (44, 45, 47). Furthermore, the study by Mao et al. identified two molecular predictive markers for response to celecoxib: High baseline Ki-67 and a high ratio of COX-2 to 15-PGDH mRNA (45). This work is helping us move towards personalized prevention, with selection based on smoking status and on biomarkers such as Ki-67 and the ratio of COX2 to 15-PGDH; similar changes are occurring in the treatment of advanced lung cancer, where small subsets of patients such as those with *EGFR* mutations or *EML4-ALK* translocations are benefiting from specific targeted treatments.

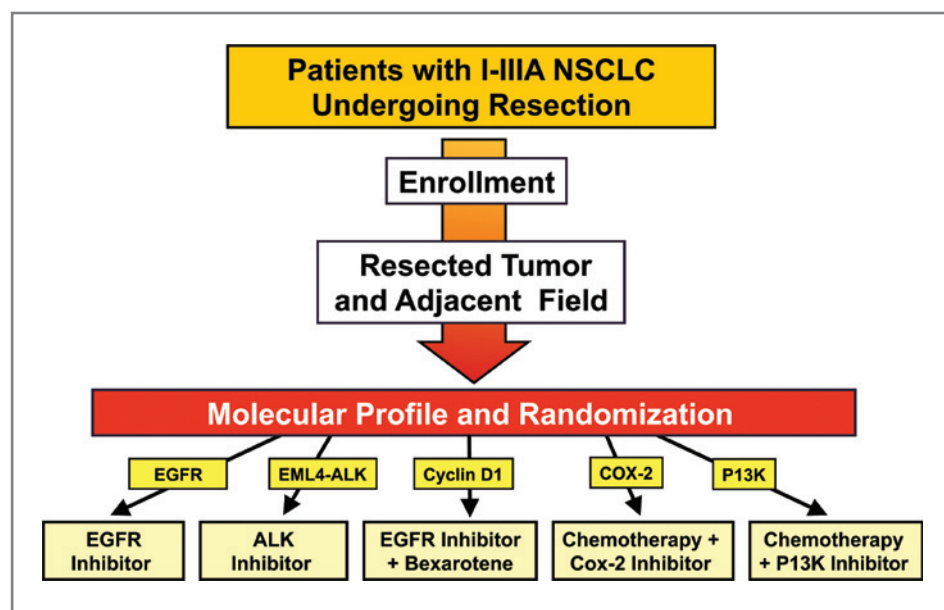
Although we developed the BATTLE program initially for lung cancer therapy, it could be extended to the prevention setting, serving as a model of trial design, with its innovative Bayesian statistical design and emphasis on predictive and prognostic biomarker discovery. BATTLE provides a platform for target discovery via its analyses of multiple blood and tissue biomarkers, and it is a source of experi-

ence with targeted agents such as sorafenib, erlotinib, and bexarotene. Sorafenib is an oral multikinase inhibitor with potent antiangiogenic activity and was active in patients with *KRAS* mutations in BATTLE. BATTLE tested bexarotene (targeting the retinoid X receptor) combined with erlotinib (targeting *EGFR*), recently shown to have activity in refractory non-small-cell lung cancer (102). This intervention was designed for the prespecified hypothesis that patients with high cyclin D1 expression would do better on the arm with these combined oral agents. Results confirmed this hypothesis, suggesting the potential of the combination in lung cancer prevention targeting individuals with cyclin D1 overexpression. BATTLE discovery efforts have identified *EGFR* and epithelial to mesenchymal transition (EMT) signatures predicting disease control with erlotinib in patients with *EGFR* wild-type tumors (103). The lessons we have learned from the BATTLE therapy program may help us in studying sorafenib, erlotinib, and bexarotene plus erlotinib for cancer chemoprevention.

The first approach toward personalized chemoprevention in the lung should occur in the tertiary prevention setting, which is the first reverse step after cancer and involves patients with a history of resected lung cancer. These patients are at high risk for recurrence and SPTs, which can be histologically indistinguishable. Histologically normal tissues near a tumor often have molecular abnormalities that may lead to a second cancer (104).

We recently completed accrual to an ongoing prospective study involving serial bronchoscopies with biopsies over a 36-month period in 41 resected lung cancer patients, following these patients closely for recurrence or SPTs. Plans for this study include creating a biological risk model, validating promising risk markers from other studies (27), and carefully studying and comparing histologically normal tissue adjacent to the site of resected cancer, tumor

**Figure 3.** Schema for a personalized trial of tertiary chemoprevention/adjuvant treatment. The tumor and adjacent field will undergo biomarker analysis, and patients will be grouped based on marker status. In the *EGFR* group, patients with *EGFR* mutations will receive *EGFR* inhibitors. Patients with *EML4-ALK* translocations by FISH will receive an inhibitor of the fusion protein such as crizotinib. The cyclin D1 group will include patients with cyclin D1 overexpression. Patients with a high ratio of COX-2 to 15-PGDH or high expression of COX-2 will receive a COX-2 inhibitor in combination with chemotherapy. The PI3K group will include patients with either PI3K amplifications or mutations or PTEN loss.



tissue, and normal tissue from patients without an SPT or recurrence. Preliminary data from this project suggest that a PI3K activation signature adjacent to the resected tumor may predict recurrence/SPT and that this signature could be targeted in tertiary prevention. The data we generated in these analyses could help to guide personalized prevention strategies (74, 104).

We propose a trial of personalized chemoprevention in the tertiary setting of resected lung cancer to be based on all that we have learned from our BATTLE and biological risk-modeling experience. We call this proposal the BATTLE-Prevention (BATTLE-P) trial (Fig. 3). We propose to recruit patients with resected lung adenocarcinoma and to conduct biomarker analyses of their tumors and adjacent epithelium. We would then assign patients to various treatment groups, as determined by the molecular drivers of lung tumorigenesis. Patients whose tumors are driven by *EGFR* mutations could be assigned to treatment with an *EGFR* inhibitor such as erlotinib or gefitinib; this is an example of reverse migration based on *EGFR* tyrosine kinase inhibitor (TKI) activity in advanced *EGFR*-mutant tumors. This assignment would be reasonable despite recently presented results of a trial called BR-19 showing no evidence of benefit with adjuvant gefitinib in resected lung cancer patients—only a small number of BR-19 patients had tumors with *EGFR* mutations (105). In contrast to BR-19, a recent retrospective analysis from Memorial Sloan-Kettering in 167 patients with mutated *EGFR* tumors found that the 56 patients who received adjuvant *EGFR* TKI had an improved 2-year disease-free survival rate (vs. no adjuvant *EGFR* TKI; HR = 0.53,  $P = 0.06$ ; ref. 106). [The ongoing phase III adjuvant trial of erlotinib in *EGFR*-mutant patients (RADIANT) should help clarify this issue.] In advanced lung cancer, overexpression of cyclin D1 is predictive of response to a combination of erlotinib and bexarotene (102, 107); patients whose resected tumors overexpressed cyclin D1 could be treated with this combination. Patients with a high ratio of COX-2 to 15-PGDH mRNA or high COX-2 expression would receive celecoxib plus chemotherapy, as studies in both prevention (45) and advanced malignancy (55, 56) suggest that these markers may predict benefit from COX-2 inhibitor-based treatment. Patients with *EML4-ALK* translocations would receive an *ALK* inhibitor, and those with PI3K pathway alterations (69, 108) would receive a PI3K/Akt inhibitor (21). Primary endpoints would be recurrence and SPTs. Secondary endpoints would be tolerability, biomarker modulation, and correlation of biomarker modulation with outcome. Dosing and informative biomarkers for patient selection must be optimized before this trial can begin; nevertheless, this type of trial design will likely become more common in the future, as our knowledge of the biology of lung tumorigenesis improves.

The reverse migration of these concepts of personalized therapy can revolutionize cancer prevention. It is worth noting that such migrations can go both ways—agents used for chemoprevention may be effective treatment options for advanced disease. The COX-2-selective inhi-

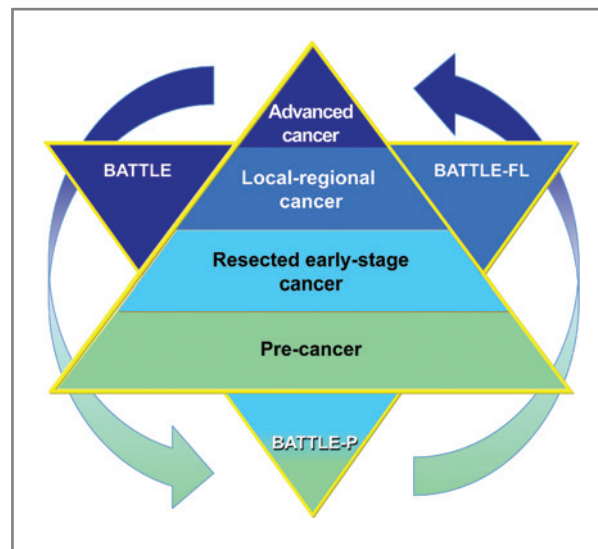


Figure 4. Schema for a comprehensive BATTLE strategy against all stages of carcinogenesis, from advanced malignancy to premalignancy (precancer). BATTLE (top left) is our completed trial in advanced cancer. BATTLE-Frontline (BATTLE-FL, top right) is our developing trial in locoregional disease. BATTLE-P (bottom) comprises the adjuvant (resected, early-stage cancer) and premalignancy/precancer settings.

bitor celecoxib has been studied for cancer prevention (22) and more recently for the treatment of advanced cancer (109, 110). Metformin has also been studied for cancer prevention and may have a future role in cancer treatment (111).

## Conclusions

Although we have much to learn, our current knowledge of the biology of lung cancer will allow us to design and implement trials that will begin to address the problem of personalized lung cancer prevention. Information from personalized lung cancer therapy trials such as BATTLE can be applied via reverse migration to chemoprevention in the primary, secondary, or tertiary prevention setting, as shown in Figure 4. The recently described concept of "cancer interception" highlights reverse migration as an active approach for cancer prevention drug development based on the tremendous advances in the biology and understanding of invasive cancer (112). Tertiary prevention trials are a good starting point for testing personalized chemoprevention because of their more easily defined patient populations and endpoints. Later, this approach could be refined for primary and secondary prevention studies. Differential effects of chemopreventive agents in former versus current smokers should be carefully considered. A better understanding of risk factors such as inflammation (46, 113) and how to alter them will guide future prevention studies. For example, recent studies of celecoxib and iloprost are currently examining associations between modulation

of targets and molecular risk and benefit and thus represent important steps toward personalized secondary chemoprevention in patients most likely to benefit from the intervention (44, 47).

An ideal prevention paradigm would select an intervention based on a personal risk profile that includes both clinical and molecular parameters. There would be a personalized approach for every patient. Patients at low risk should receive counseling on lifestyle modifications. Those at moderate risk could be candidates for more intensive screening in addition to lifestyle counseling, and high-risk patients would receive targeted, personalized chemoprevention in addition to screening. Mobilizing its knowledge and technology to move into settings of

defined cancer risk, the BATTLE for lung cancer chemoprevention is on.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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## The BATTLE to Personalize Lung Cancer Prevention through Reverse Migration

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